Attorney Docket No. TMT-10902/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Michael T. Trese et al.

Serial No.: 10/068,314 Group Art Unit: 3763

Filed: February 6, 2002 Examiner: Matthew F. DeSanto

For: METHOD FOR VITREOUS LIQUEFACTION

DECLARATION OF MICHAEL K. HARTZER, Ph.D.

I, Michael K. Hartzer, hereby declare as follows:

1. Currently I am Director of the Trumbull Ophthalmic Research Laboratory at William Beaumont Hospital Research Institute, Royal Oak, Michigan. I have held this position since January 1991. In addition, I have been Director of Research and Development at NuVue Technologies Inc. since May 2000. Prior to these positions, I was a professor of various grades at the Eye Research Institute, Oakland University, Rochester, Michigan from September 1985 until July 2000.

2. I hold Ph.D. and B.S. degrees from Iowa State University. I also have completed post-doctoral training as a Fellow in Ophthalmology and Cell Biology at the Bascom Palmer Eye Institute, University of Miami School of Medicine from July 1984 through September 1985. I have authored or co-authored over 25 scientific publications and over 100 published abstracts in this field. I have been carrying out research on ophthalmic disorders for approximately 12 years.

3. I am a co-inventor on the above-identified patent application, U.S. Patent Application Serial No. 10/068,314 ("the Application") and have read the Office Action dated December 20, 2002 ("the Office Action"). I have also reviewed and am familiar with the reference cited in the Office Action, M.T. Trese, G.A. Williams and M.K. Hartzer, "A New

Approach to Stage 3 Macular Holes" *Ophthalmology* 107(8), 2000, pp. 1607-1611, of which I am a co-author.

4. I understand that pending claims 1-24 of the Application have been rejected under 35 U.S.C. §102(b) as being anticipated over the *Ophthalmology* Vol. 107 article which I co-authored with M.T. Trese and G.A. Williams. I state as a co-author of Trese et al. and having subsequently worked on the current invention that at the time that Trese et al., it was unknown to me and my co-inventors that liquefaction of vitreous gel in the human eye at a dose of 0.4 units of plasmin was highly variable and represented our understanding of the liquefaction process at that time.

5. Subsequent to the publication of Trese et al., I have modified the activation procedure for plasminogen. The work done in 1999 and published in Trese et al. used a 1:1 molar ratio of streptokinase to plasminogen. A 1:1 molar ratio of streptokinase to plasminogen produced a final product that was essentially all streptokinase-plasminogen complex. Subsequent to the publication of Trese et al., I participated in experiments that used a 0.1:1 molar ratio of streptokinase to plasminogen that resulted in a final product containing 90% plasminogen and only 10% streptokinase-plasmin complex. I have strong experimental evidence that plasmin has much higher biological activity within the vitreous than does the streptokinase-plasmin complex.

6. I believe the reason for the higher biological activity of plasmin relative to the streptokinase-plasmin complex is that the complex represents a much larger molecule than plasmin. Such proteins have three-dimensional structures, often the sites on the substrate proteins, such as fibrinogen, laminin, and fibronectin, that contain the correct amino acid sequence to be recognized and cleaved by the enzyme are not on the surface of the molecule and instead are located in a pocket or crevice. The size and stearic constraints associated

with the streptokinase-plasmin complex limits the access of this complex the ability of the streptokinase-plasmin complex to access crevices and pockets within the vitreal substrate.

7. As a result of the formation of free plasmin that has a higher biological activity than the streptokinase-plasmin complex, it is possible according to the present invention to consistently perform liquefaction of the vitreous gel at plasmin doses of 0.4 units or less. The invention of claims 1-24 varies from the teaching of Trese et al. in that in Trese et al. streptokinase-plasmin complex was formed and not free plasmin which, as detailed above, has a greater biological activity toward liquefaction of the vitreous gel.

8. Based on the above considerations, I do not believe that Trese et al. teaches vitreous liquefaction in a human eye at a plasmin dose of less than 0.4 units.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Michael K. Hartzer, Ph.D.

Date: 5/9/03

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